REMARKS

Claim 5 has been amended. New Claims 14-20 have been added. Thus, Claims 5-20 are presented for further examination.

Applicants submit that no new matter was added by the amendments, and that support for the amendments can be found throughout the specification. Support for the amendment to Claim 5 and new Claims 14-19 can be found, for example, in the claims as originally filed and paragraphs [0199], [0336], [0362], [0407], and Example 18 starting at paragraph [0529].

Applicants thank the Examiner for the review of the instant application. The rejections of the presently pending claims are respectfully traversed.

Rejection Under 35 U.S.C. §101 – Utility

The PTO maintains its rejection of Claims 5-13 under 35 U.S.C. § 101 as lacking utility for the reasons set forth on pages 3-4 of the previous Office Action. The PTO asserts that the data of Example 18 are insufficient because "[t]here is no guidance in the specification as to how high the levels are," and the first Grimaldi declaration "does not teach the level of reproducibility or the level of reliability of the results." Office Action at 3-4. The PTO also states that "[n]either the specification nor the declarations provide any evidence that indicates what the differences were or whether the results were statistically significant." Office Action at 4. The PTO asserts that Applicants have provided "no indication of the nature or number of samples that were used." Office Action at 4. The PTO concludes that the disclosure "does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases." Office Action at 4.

Finally, the PTO states that whether or not increased levels of PRO1106 mRNA correlate with increased levels of PRO1106 protein is not an issue. The PTO concludes that the declarations and cited references do not establish a substantial utility for the claimed PRO1106 nucleic acid molecules (presumably the PTO meant claimed polypeptides).

In the Advisory Action mailed on January 13, 2005, the Examiner further asserts that "Applicants have not taught what kind of esophageal tumors could be diagnosed." Also, the Examiner argues that there is no teaching of the baseline levels of expression or the numerical values for the levels of overexpression and underexpression. The Examiner states that the skilled artisan would not know if such differences were due to aneuploidy.

Applicants respectfully disagree and submit that for the reasons stated below, the claimed PRO1106 polypeptides have a credible, substantial, and specific utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the

art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill**

in the art would be convinced, to a reasonable probability, that the asserted utility is true. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed polypeptides have utility as diagnostic tools for cancer, particularly esophageal cancer. Applicants are not asserting that the claimed polypeptides necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1106 polypeptide is more highly expressed in esophageal tumor tissue than in normal esophagus tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO1106 polypeptide is decreased in normal esophagus tissue than in cancerous esophageal tissue, it is likely that the PRO1106 polypeptide is differentially expressed in esophageal tumor and is therefore useful as a diagnostic tool to distinguish tumor from normal tissue.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the significance and the reliability of the evidence reported in Example 18, and states that these data do not allow a skilled artisan to differentiate amongst expression levels in order to diagnose any disease;

2. The PTO asserts that one of skill in the art "would not know whether the gene is actually more highly expressed in certain tumors or whether the 'overexpression' is due to aneuploidy."

3. Finally, the PTO states that whether or not increased levels of PRO1106 mRNA correlate with increased levels of PRO1106 protein is not an issue.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, whether or not aneuploidy is involved is irrelevant, what is important is that there are different levels of mRNA in normal cells compared to the corresponding tumor cells, which provides a utility for the differentially expressed nucleic acid and polypeptide. Third, Applicants submit that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO1106 protein is likely differentially expressed in certain tumors. This provides utility for the PRO1106 and related proteins as cancer diagnostic tools. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence to establish that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not statistical or absolute certainty.**

Applicants have established that the Gene Encoding the PRO1106 Polypeptide is Differentially Expressed in Esophageal Cancer compared to Normal Esophagus Tissue

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1106 polypeptide in esophageal tumors is insufficient.

The gene expression data in the specification, Example 18, shows that the mRNA associated with protein PRO1106 was more highly expressed in esophageal tumor tissue than in normal esophagus tissue. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1106 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. In support, Applicants previously submitted as Exhibit A, a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue

and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The PTO argues that Example 18 is insufficient because it does not teach how high the expression level is, what the level of reproducibility or reliability is, whether the results are statistically significant, or the nature or number of samples that were used. The PTO also argues that one cannot determine if the observed differential expression is due to aneuploidy. The PTO concludes that the disclosure would not enable one of skill in the art to differentiate amongst expression levels to diagnose any disease.

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Mr. Grimaldi's opinion with regard to his statement that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the genes of interest "can be used to differentiate tumor from normal." Together, these statements establish that there is at least a two-fold difference in expression, and that the results are reliable enough that they can be used to distinguish tumor from normal tissue. Finally, Applicants submit that whether this differential expression is due to aneuploidy is not relevant to whether the difference in expression can be used to distinguish tumor from normal tissue.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1106 cDNA between esophageal tumor tissue and normal esophagus tissue. Therefore, it follows that expression levels of the PRO1106 gene can be used to distinguish esophageal tumor tissue from its normal tissue counterpart. The PTO has not offered any significant arguments or evidence to the contrary.

As Applicants explain below, it is more likely than not that the PRO1106 polypeptide is also differentially expressed in esophageal tumor tissue, and can therefore be used to distinguish esophageal tumor tissue from normal esophagus tissue. This provides utility for the claimed polypeptides.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1106 polypeptide in esophageal tumor, it is more likely than not that the PRO1106 polypeptide is differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (previously attached as Exhibit B). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D. (previously attached as Exhibit C), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 1) and (4th ed. 2002) (previously submitted in the response filed on December 17, 2004 as Exhibit 2)). Figure 9-2 of Exhibit 1 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 1 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 1 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 1 at 453 (emphasis added). Thus, as established in Exhibit 1, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In the 4th Edition of Alberts et al., Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression.

The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." 4th Edition of Alberts et al. at 302 (emphasis added). Similarly, Figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." 4th Edition of Alberts et al. at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." 4th Edition of Alberts et al. at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 2) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Also, Applicants have previously submitted additional exemplary references that provide further support for Applicants' position. For example, Applicants have previously submitted Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004; and Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), all of which support Applicants' assertion that gene expression more likely than not correlates with protein expression.

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

In the Advisory Action mailed on January 13, 2005, The Examiner states that the skilled artisan would not know if differences in expression in tumor compared to non-tumor cells were due to aneuploidy. Respectfully, whether or not aneuploidy or gene amplification leads to

differential gene expression, as seen here, is irrelevant. Specifically, whether the differential mRNA expression of the PRO1106 gene reported in Example 18 is due to an increase or decrease in copy number, or alternatively due to an increase or decrease in transcription rates is simply not relevant. Applicants have provided reliable evidence that the PRO1106 mRNA is differentially expressed in certain tumors. Whether this differential expression is due to changes in gene copy number, transcription rates, a combination of the two, or some other known or unknown cellular mechanism is simply not relevant to Applicants' asserted utility.

The fact that the PRO1106 nucleic acids and polypeptides are differentially expressed confers utility regardless of whether aneuploidy was involved. The Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides. (*See, e.g.,* U.S. Patent No. 6,414,117 and U.S. Patent No. 6,124,433, attached hereto as Exhibits 3 and 4.)

As discussed above, Applicants respectfully disagree with the PTO's position that whether or not increased levels of PRO1106 mRNA correlate with increased levels of PRO1106 protein is not an issue. Because it is more likely than not that the PRO1106 protein is also differentially expressed in certain tumors, the protein can be used as a diagnostic tool for cancer.

Thus, the PTO's rejection of the second Grimaldi Declaration and Polakis Declaration because they are viewed as insufficient or irrelevant is misplaced. Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1106 mRNA is more highly expressed in esophageal tumor tissue than in normal esophagus, the PRO1106 polypeptide will have the same expression pattern. This differential expression of PRO1106 and related polypeptides make them useful as diagnostic tools for cancer.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed polypeptide is differentially expressed in certain tumors and that the claimed polypeptides can be used as diagnostic tools. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed polypeptides can be used as diagnostic tools for cancer, particularly esophageal cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed polypeptides related to PRO1106. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1106 gene and polypeptide in esophageal tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene for the PRO1106 polypeptide is more highly expressed in esophageal tumor tissue than in normal esophagus. These data are strong evidence that the PRO1106 gene and polypeptide are associated with esophageal tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1106 gene and polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly esophageal tumor, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has generally asserted three arguments to support its conclusion that the differential expression of PRO1106 is not sufficient to establish utility for the claimed polypeptides: (1) the PTO has challenged the significance and the reliability of the evidence reported in Example 18; (2) the PTO asserts that one of skill would not know whether the differences in expression were due to aneuploidy; and (3) the PTO states that whether or not increased levels of PRO1106 mRNA correlate with increased levels of PRO1106 protein is not an issue. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the relative difference in expression levels, the disclosed nucleic acids and corresponding polypeptides have

utility as cancer diagnostic tools. The PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration.

Second, Applicants have demonstrated that it is not necessary to know the cause or consequence of the differential expression of PRO1106 nucleic acids and polypeptides in certain tumors in order to use them as diagnostic tools for cancer.

Third, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reason or evidence to question these declarations and supporting references. One of skill in the art will recognize that polypeptides differentially expressed in certain cancers have utility as diagnostic tools for cancer.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because the PRO1106 gene and polypeptide are differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of polypeptides.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides relating to PRO1106 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also maintains the rejection of Claims 1-13 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention. The PTO argues that the limitation "wherein said isolated polypeptide is more highly expressed in esophageal tumor tissue than in normal esophagus tissue or wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in esophageal tumor than in normal esophagus tissue" is not a functional limitation. The PTO argues that there is no nexus between the polypeptide's structure and the recited function. Finally, the PTO argues that one skilled in the art would not know how to engineer a sequence such that it is overexpressed in certain tissues.

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

As amended, the pending claims are related to isolated polypeptides having at least 99% amino acid sequence identity to polypeptides related to SEQ ID NO:58, and which satisfy the limitation "wherein said isolated polypeptide is more highly expressed in esophageal tumor tissue than in normal esophagus tissue or wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in esophageal tumor than in normal esophagus tissue" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:58 in an esophagus tissue sample."

Applicants submit that the claimed polypeptides are enabled, as one of skill in the art would know how to make and use them. Applicants submit that it is well-established in the art

how to make polypeptides which have at least 99% amino acid sequence identity to the disclosed sequence related to SEQ ID NO:58. Applicants have disclosed how to determine if the claimed polypeptides or encoding nucleic acids are differentially expressed in esophageal tumors compared to normal esophagus. Applicants have also disclosed how to make antibodies to the polypeptide of SEQ ID NO:58, and given the high amino acid sequence homology of the claimed polypeptides, one of skill in the art would know how to make antibodies to SEQ ID NO:58 from the claimed polypeptides. Thus, one of skill in the art would know how to make the claimed polypeptides.

As discussed above, Applicants submit that they have established that one of skill in the art would believe that it is more likely than not that the PRO1106 gene and polypeptide are differentially expressed in esophageal tumors such that they can be used as cancer diagnostic tools. Given the disclosure in the specification and the level of skill in the art, a skilled artisan would know how to use the claimed polypeptides as diagnostic tools. For example, polypeptides which have at least 95%, 98% or 99% amino acid sequence identity to the disclosed sequences and are "more highly expressed in esophageal tumor than in normal esophagus tissue..." can be used as diagnostic tools since the claimed polypeptides or their encoding nucleic acids are differentially expressed in tumors. Other claimed polypeptides which have at least 95%, 98% or 99% amino acid sequence identity to the disclosed sequences and "said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:58 in an esophagus tissue sample," are also useful diagnostic tools. Because the polypeptide of SEQ ID NO:58 is most likely differentially expressed in esophageal tumors, antibodies for specific detection of this polypeptide in esophagus tissue samples are useful diagnostic tools.

Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO maintains the rejection of Claims 5, and 12-13 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement for the reasons set forth on

pages 6-7 of the previous Office Action. Briefly, the PTO asserts that there is no connection between the 'functional' limitation and the structure of the claimed polypeptides." Thus, according to the PTO, Applicants have not taught distinguishing identifying characteristics of the genus.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

As amended, the pending claims are related to isolated polypeptides having at least 99% amino acid sequence identity to polypeptides related to SEQ ID NO:58, and satisfy the limitation

"wherein said polypeptide is more highly expressed in esophageal tumor than in normal esophagus tissue or wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in esophageal tumor than in normal esophagus tissue" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:58 in an esophagus tissue sample."

Applicants maintain that there is no substantial variation within the species which fall within the scope of the amended claims, which require at least 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO:58. Applicants note that the pending Claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO:58 in esophagus tissue samples.

In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides with at least 99% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in esophageal tumors, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO:58 in esophagus tissue samples. Like Example 14, the genus of polypeptides that have at least 99% amino acid sequence identity to the disclosed sequences will not have substantial variation.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No: 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502 which are attached hereto as Exhibits 5-10.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:58, by specifying a high level of amino acid sequence identity, by describing how to test for differential expression of the polypeptide and encoding nucleic acid, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Discussion of Previous Rejection under 35 U.S.C. §102 – Anticipation

In the first Office Action dated May 17, 2004 the PTO rejected Claims 1-4 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,573,095 (the '095 patent). The PTO argued that the '095 patent disclosed a sequence that was 97% identical to SEQ ID NO:58.

Applicants submit that new Claims 15, 16, 19 and 20, reciting 98% and 99% identity, respectively, are not anticipated by the '095 patent.

Furthermore, amended Claim 5 and new Claim 14 are not anticipated by the '095 patent because Applicants were in possession of SEQ ID NO:58 prior to the effective publication date of the '095 patent.

Attached herewith is the Declaration of Audrey Goddard, Paul J. Godowski, J. Christopher Grimaldi, Austin L. Gurney and William I. Wood under 37 C.F.R. §1.131 (prepared for co-pending U.S. Application No. 10/063,566; referred to hereafter as "the Declaration of Goddard et al."), which establishes that the presently claimed invention antedates the effective date of the '095 patent. The Declaration of Goddard et al. establishes that the presently claimed subject matter was conceived prior to the earliest effective filing date of the '095 patent, April 29, 1998, and diligently reduced to practice thereafter. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejections under 35 USC §102(e) be withdrawn.

As set forth in 37 C.F.R. § 1.131, a patent applicant "may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based." *See also*, M.P.E.P. § 715. "The affidavit or declaration must state FACTS and produce such documentary evidence and exhibits in support thereof as are available to show conception and completion of the invention in this country ... at least conception being at a date prior to the effective date of the reference." *See* M.P.E.P. § 715.07 (emphasis in original). The showing of facts must be sufficient to show "conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent (actual) reduction to practice." *See id.*

The '095 patent is based upon U.S. Application No. 09/312,283 filed on May 14, 1999, which was a continuation-in-part of U.S. Application No.09/188,930, filed on November 9, 1998, which application was a continuation-in-part of U.S. Application No. 09/069,726, filed on April 29, 1998. Therefore, the earliest possible effective filing date of the '095 patent is April 29, 1998. The '095 patent is cited as a 102(e) reference because it allegedly discloses antibodies to the amino acid sequence of SEQ ID NO:339, which the PTO argues is 97% identical to the polypeptide of SEQ ID NO:58 from the instant application. However, as set forth below, Applicants were in possession of SEQ ID NO:58 prior to the effective date of the '095 patent.

The Declaration and attached Exhibit A demonstrate that the claimed subject matter, particularly a polypeptide having the sequence of SEQ ID NO:58, was conceived by Applicants prior to April 29, 1998. Furthermore, as evidenced by the Declaration and Exhibits B-C, Applicants exhibited diligence in reducing the subject matter of the claims to practice from at least just prior to the '095 patent effective date, by performing various assays to confirm the function of the polypeptide.

In view of the above, Applicants respectfully submit that the amended and new claims are not anticipated by the '095 patent under 35 U.S.C. §102(e).

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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